The Metric Physical Map of Human Chromosome 19: An Entrez into Genomic Sequencing

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We have constructed a cosmid-based, metric physical map that spans approximately 95% of the euchromatin. A high-resolution fluorescence *in situ* hybridization technique was used to obtain distance and relative order information between nearly 270 selected cosmids along the chromosome. This FISH map provided the 'to-scale' metric upon which to anchor contigs. The average distance between reference cosmids is <200 kb (range: 50-600 kb). By identifying large insert clones (including YACs, BACs, PACs and P1s) that span gaps between ordered cosmid contigs, the total number of ordered 'islands' has been reduced to 32. To localize genes, genetic markers and ESTs on the map, high-density filter arrays of the cosmids were hybridized. Using a new spotting robot and 384-pin tool, we are currently producing 6x6x384 filters containing 13,824 cosmids per 8x12 cm substrate. Computer-aided image analysis of filters links filter position directly to our relational database. Over 500 markers including genes, cDNAs, ESTs and poly-morphic markers have been localized, >400 of which have been incorporated into the ordered map. Selected cosmids were digested with *Eco*RI to produce an ordered set of *Eco*RI restriction maps (see Olsen, et al. abstract) from which minimally overlapping cosmids are selected for genomic sequencing. We are scaling our sequencing facility to take advantage of these ordered clones to provide high-throughput, high accuracy sequence for all of chromosome 19, as well as other targets of interest. Integral to our expanded sequencing effort is newly developed software designed to track and manage DNA sequencing sample information as well as robotics for M13 template generation. To date, we have completed 650 kb of genomic sequence in regions associated with DNA repair and disease susceptibility. Current genomic sequencing includes a 1-Mb region in q13.1 encompassing the CNF gene, 300 kb in p12 encompassing MEF2B, two clusters of olfactory receptor genes located in p13.1 and p13.2, and a 150 kb region surrounding the HHR23A DNA repair gene in p13.2. (Work was performed by LLNL under the auspices of the U.S. DOE under contract No. W-7405-ENG-48.)